IN THE UNITED STATES DISTRICT COURT
FOR THE EASTERN DISTRICT OF VIRGINIA
ALEXANDRIA DIVISION

GEORGIA TORKIE-TORK,	§	
Plaintiff,	§	
	§	**No. 1:04cv945**
vs.	§	
	§	
WYETH,	§	
Defendant.	§	

PLAINTIFF'S OPPOSITION TO
DEFENDANT'S CONSOLIDATED *DAUBERT* MOTION

Wyeth has raised the same challenges repeatedly, to little avail. Wyeth's attack on differential diagnosis as an appropriate methodology for isolating hormone therapy as a cause of a plaintiff's breast cancer has been rejected in five separate trial-set cases by the MDL court, by the United States Court of Appeals for the Eighth Circuit and by courts presiding over 11 trial-set cases in four different states. Wyeth's attempt to exclude the testimony of plaintiff's liability experts has also been repeatedly rebuffed. While the MDL magistrate judge did recently limit the plaintiff's regulatory experts' testimony, the limit precluded only ultimate opinions on whether Wyeth's failure to test breached the standard of care; otherwise, the testimony was not restricted.

Of course, this Court will make its own judgment on the reliability of expert testimony, guided by Federal Rule of Evidence 702 and the Supreme Court's holding in *Daubert v. Merrell Dow Pharms., Inc.*, 509 U.S. 579 (1993). "Rule 702 was intended to liberalize the introduction of relevant evidence." *Westberry v. Gislavid Gummi AB*, 178 F.3d 257, 261 (4th Cir. 1999). The former requirement that the principles upon which expert testimony is based must be "generally accepted" in the scientific community was superseded by Rule 702. *Daubert*, 509 U.S. at 587-89. Today, expert testimony is admissible so long as the expert's methodology or reasoning is

scientifically valid and can be reasonably applied to the facts of the case. *Id.* at 592-93. The Court's role is not to determine whether the testimony is "irrefutable or certainly correct." *Westberry*, 178 F.3d at 261. And "exclusion is the least favored means of rendering questionable scientific evidence ineffective." *Cavallo v. Star Enterprise*, 100 F.3d 1150, 1158 (4th Cir. 1996), *cert. denied*, 522 U.S. 1044 (1998). Rather, "[v]igorous cross-examination, presentation of contrary evidence, and careful instruction on the burden of proof are the traditional and appropriate means of attacking shaky but admissible evidence." *Daubert*, 509 U.S. at 596.

I. PLAINTIFF'S SPECIFIC CAUSATION EXPERT: DR. MICHAEL WERTHEIMER

Dr. Wertheimer's methodology and reasoning are scientifically valid. Wyeth claims that differential diagnosis is inappropriate in the breast cancer context because we do not know all the causes of breast cancer. But plaintiff is not arguing "cause" in the sense that Wyeth or its experts are. Plaintiff does not contend that hormone therapy "initiated" the first bad cell that ultimately became cancerous. Plaintiff admits that much is still unknown about what causes that first abnormality. Rather, plaintiff argues that hormone therapy "promoted" the growth of her cancer. Since her cancer was hormone-dependent, it required hormones to grow. Combination hormone therapy (or E+P)[1] provided the fuel that enabled her hormone-dependent abnormal cells to proliferate and divide and eventually become a malignant tumor.[2] Without Prempro, whatever abnormalities were present in plaintiff's breast at menopause would never have developed into

[1] "Combination hormone therapy" refers to the combination of estrogen (E) with progestin (P) and is often referred to as "E+P." Unfortunately, E+P has far more deleterious effects on the breast than E alone. Plaintiff ingested Wyeth's Prempro, an E+P product.

[2] The linear progression of cancer from the first abnormal cell to an invasive malignancy is best exemplified by the model diagram attached as Exhibit 1, which appears in Wyeth's own documents. (Ex. 2- PX 6579A).

clinical cancer but would have shrunk or regressed.[3] Indeed, when the sales of E+P plummeted in 2002 after the world learned the truth about the breast cancer risk from the Women's Health Initiative Study (WHI), an estimated 17,500 women each year stopped developing breast cancer solely because these hormone-dependent abnormalities received no fuel to promote their growth into cancer.[4]

If a tumor tests positive for the presence of hormone receptors, as plaintiff's cancer did, we know the tumor required hormones to grow.[5] "But for" hormones, the abnormal cell or groups of cells (benign lesions) would have died, shrunk, regressed or remained dormant. Thus, combination hormone therapy was a "but for" cause of plaintiff's breast cancer if plaintiff was no longer producing sufficient natural hormones to fuel the growth of the cancer. Dr. Wertheimer determined that plaintiff was no longer producing sufficient natural hormones, as revealed by her menopausal symptoms. It was thus more likely than not that E+P was essential to the development of her cancer.

This process of differential diagnosis is precisely what the Eighth Circuit found valid in *Scroggin v. Wyeth*, 586 F.3d 547 (8th Cir. 2009), *cert. denied*, 130 S. Ct. 3467 (June 21, 2010). The appellate court affirmed a judgment of the MDL court rejecting the same arguments Wyeth has made here with respect to the methodology of plaintiff's case specific expert, Dr. Elizabeth Naftalis about plaintiff, Donna Scroggin's hormone receptor-positive tumors.

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[3] Berry and Ravdin (Ex. 3 - PX ML 4775) at p. 2 (…[S]topping menopausal hormone therapy removes the fuel that is promoting the growth of some tumors. The growth of these tumors preferentially ER-positive tumors may slow or stop entirely, or the tumors may even regress); Chleblowski (Ex. 4 - PX ML 4881) at p. 10 (The rapid decrease in breast cancers once women stopped taking E+P "suggests that withdrawal of estrogen-plus-progestin therapy leads to a regression of preclinical cancers.")

[4] Kerlikowske (Ex. 5 - PX ML 4854) at p. 5.

[5] Wyeth's website (Ex. 6 - PX 10555) at p. 4; National Cancer Institute (Ex. 7 - PX 8426A); Oncolink (Ex. 8 - PX 8426B).

> Knowing that Scroggin's breast cancer was hormone-dependent, Dr. Naftalis' differential diagnosis sought to determine the cause of Scroggin's breast cancer by ruling out the two possible sources of these hormones: (1) Scroggin produced the hormones herself, or (2) they came from the hormone replacement therapy she had taken for the past eleven years.
> * * *
> We find unpersuasive the contention that Dr. Naftalis' testimony should not have been admitted because Scroggin has some breast cancer risk factors and a family history of breast cancer. Dr. Naftalis sufficiently established that hormones were necessary to the development of Scroggin's tumors and conducted her differential diagnosis from this starting point.
> * * *
> Thus, Dr. Naftalis ruled out the other possible cause of Scroggin's breast cancer [endogenous hormones], and her expert testimony was properly admitted.

Id. at 566-67

A. General Causation – E+P Causes Breast Cancer by Promoting Abnormal Cells and Benign Lesions into Malignant Tumors.

Wyeth makes numerous arguments suggesting E+P does not adversely affect the breast. Yet, Wyeth has not challenged the admissibility of testimony by plaintiff's general causation experts, Dr. Graham Colditz[6] and Dr. Don Austin.[7] The evidence that E+P causes breast cancer is too strong for such a challenge. Every type of human study has confirmed the causal link, including randomized clinical trials and myriad observational studies (including both cohort and case control studies). In fact, 45 epidemiological studies reported in peer-reviewed medical journals show a statistically significant relative risk ("RR") that exceeds 2.0 (i.e., more than a doubling of the risk) of breast cancer from ingestion of E+P.[8] Indeed, multiple studies confirm statistically significant relative risk statistics for women just like Georgia Torkie-Tork above 2.0,

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[6] Ex. 9 - Deposition designations for Dr. Graham Colditz's preservation deposition. Wyeth raises no *Daubert* challenge to Dr. Colditz's testimony which confirms that E+P can cause breast cancer generally.

[7] Wyeth has challenged Dr. Austin's liability testimony (that Wyeth could have performed a breast cancer study earlier) but not Dr. Austin's testimony that E+P causes breast cancer.

[8] Ex. 10 - Chart of 45 epidemiological studies which show a doubling of the risk; Ex. 11 - Expert Report of Dr. Wertheimer ("Wertheimer Exp. Rpt") at 6 & n. 15; and Ex. 10 to the report. *See* also Kendall (Ex. 12) at 45:19-48:3.

3.0 and even 4.0 (i.e. older women diagnosed with hormone-dependent ductal and lobular carcinoma in situ (LCIS), Grade 1 cancer after use of E+P for several years).[9]

Epidemiological evidence showing greater than a doubling of the risk is sufficient – on its own -- to establish causation in an individual case (specific causation). *See, e.g., Manko v. U.S.*, 636 F. Supp. 1419, 1434, 1437 (W.D. Mo. 1986), *aff'd in part*, 830 F.2d 831 (8th Cir. 1987); *Daubert v. Merrell Dow Pharms., Inc.* ("*Daubert II*"), 43 F.3d 1311, 1320 (9th Cir.), *cert. denied*, 516 U.S. 869 (1995); *In re Joint Eastern & Southern Dist. Asbestos Litig.*, 52 F.3d 1124, 1128 (2d Cir. 1995). As the Third Circuit explained:

> A relative risk of "2" means that the disease occurs among the population subject to the event under investigation twice as frequently as the disease occurs among the population not subject to the event under investigation. Phrased another way, a relative risk of "2" means that, on average, there is a fifty per cent likelihood that a particular case of the disease was caused by the event under investigation and a fifty per cent likelihood that the disease was caused by chance alone. A relative risk greater than "2" means that the disease more likely than not was caused by the event.

DeLuca v. Merrell Dow Pharms., Inc., 911 F.2d 941, 958-59 (3d Cir. 1990), *disapproved on other grounds*, *Daubert v. Merrell Dow Pharms., Inc.*, 509 U.S. 579 (1993) (emphasis added); *see also Marder v. G.D. Searle & Co.*, 630 F. Supp. 1087, 1092 (D. Md. 1986) ("a two-fold increased risk…is the equivalent of the required legal burden of proof—a showing of…a probability of greater than 50%"), *aff'd*, 814 F.2d 655 (4th Cir. 1987); *Cook v. U.S.*, 545 F. Supp. 306, 308 (N.D. Cal. 1982) ("Whenever the relative risk…is greater than 2…there is a greater

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[9] Hwang (Ex. 13 - PX ML 1918) at p. 4 (Ever use of E+P for women older than 50 years old who were diagnosed with hormone-dependent cancer, RR = 3.89); Borgquist (Ex. 14 - PX 4729) at p. 4, Table III (In E+P users, ductal cancer, RR = 2.95; Grade 1 breast cancers, RR = 4.99); Reeves (Ex. 15 - PX 4580) at p. 1 (Relative risk of LCIS in E+P users= 2.82); Slanger (Ex. 16 - PX ML 4992) at p. 6 (Hormone receptor positive breast cancer, Grade 1, in continuous E+P users, RR = 3.60); Jick (Ex. 17 - PX ML 4977) at p. 1 (Increased risk among E+P users of 48 months or more = 3.10); Million Women (Ex. 18 - PX ML 79) at p. 1 (After average use of E+P for 2.6 years, RR = 2.00).

than 50% chance that a given GBS case…is attributable to vaccination, thus sustaining plaintiff's burden of proof on causation.").[10] At the last *Daubert* hearing, Wyeth's counsel acknowledged that evidence of a 2.0 relative risk is sufficient to establish specific causation.[11]

Dr. Graham Colditz, a renowned epidemiologist, ardent researcher on E+P and breast cancer and former professor of medicine at Harvard Medical School has authored over 700 peer-reviewed journal articles.[12] Dr. Colditz has testified that available epidemiological evidence has confirmed a casual relationship between E+P and breast cancer.[13] He has testified unequivocally that the causal link is now generally accepted.[14] Dr. Wertheimer concurs.[15] Dr. Don Austin is a leading epidemiologist who has published extensively on cancer incidence, and who was a principal researcher uncovering the causal relationship between unopposed E (estrogen) and endometrial cancer.[16] After reviewing a "sizable portion of the world literature," Dr. Austin testified that the epidemiological data establishes a causal relationship between E+P and breast cancer.[17] He confirmed that there is no longer any serious debate about the causative effect.[18]

The International Agency for Research on Cancer ("IARC") is the branch of the World Health Organization charged with identifying cancer-causing agents in our environment. IARC

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10 The epidemiological studies relied upon by plaintiff's experts controlled for other risk factors which confirms that the increased breast cancer risk from E+P is on top or a multiplier of the woman's existing risk factors. *See* Austin (Ex. 19) at p. 47:11-48:24.

11 Ex. 139 at 108-09.

12 Ex. 9 - Deposition of Dr. Colditz (12/18/06) at 16:24-20:3.

13 Ex. 9 at 73:19-74:5.

14 Ex. 9 at 61:5-12.

15 Ex. 11 - Wertheimer Expert Report at 7.

16 Ex. 20 – *Scroggin* Transcript at 172:1-9; 179:4-180:10; 253:4-12.

17 Ex. 20 - *Scroggin* Transcript at 176:12-177:15; 214:11-21.

18 Ex. 20 - *Scroggin* Transcript at 179:4-6.

now classifies E+P as a known carcinogen of the breast.[19] Dr. Brian MacMahon is an internationally recognized expert on breast cancer who chaired the epidemiology department at the Harvard School of Public Health. Dr. MacMahon has published that there are only three known causes of breast cancer, one of which is hormone therapy use.[20] Many other researchers have similarly confirmed a causal relationship between E+P and breast cancer.[21]

E+P causes breast cancer through promotion.[22] E+P promotes the growth of abnormal, benign cells into malignant tumors.[23] E+P causes abnormal cells in the breast to proliferate and to grow more rapidly than they would otherwise.[24] Using layman's terminology, E+P is like fertilizer on plants, and is essential to the growth of hormone-sensitive breast cancer.[25]

Many people have abnormal cells in the body at any given time.[26] In fact, autopsy studies have shown that some women who die of other causes have benign abnormal cells or

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19 Ex. 9 - Colditz Deposition at 64:8-18; 80:22-81:2; Int'l Agency for Rsch on Cancer (Ex. 21 - PX 866B) at p. 24 (There is sufficient evidence in humans for the carcinogenicity of combined estrogen-progestogen menopausal therapy in the breast).

20 Colditz (Ex. 9) at 61:16-62:16; MacMahon (Ex. 22 - ML 4196).

21 Norton (Ex. 23 - PX 8078B) at p. 33; p. 45 (WHI showed that as high as one third of the breast cancers in postmenopausal women in the past were caused by E+P; 30% of the breast cancers are caused by hormone replacement therapy); Li (Ex. 24 - PX ML 2980) at p. 1 (Results from the WHI confirm that E + P is causally related to breast cancer); Fournier (Ex. 25 - PX ML 5087) at p. 1 ("The relationship between HT use and breast cancer risk has been investigated in many epidemiological studies whose results have led to the conclusion that estrogen-progestogen menopausal treatment is carcinogenic to the breast.")

22 Weinberg (Ex. 26 - PX 1766) at p. 5 (E+P is a human tumor promoters in the breast);Wertheimer (Ex. 27) at 136:3-12, 137:9-138:14; Wertheimer (Ex. 11) at 2, 4-5; Naftalis (Ex. 28) at 17-18. Dr. Naftalis specializes in the surgical evaluation and treatment of breast disease and breast cancer. She has been certified by the American Board of Surgery, is a member of numerous breast health medical organizations and has been an associate professor in the Department of Surgery at the University of Texas Southwestern. *See* Naftalis CV (Ex. 29); Naftalis (Ex. 30) at 12-13, 30-31.

23 Ex. 9 - Colditz Deposition at 43:6-14; 48:13-49:4.

24 Ex. 9 - Colditz Deposition at 42:4-43:5; 46:18-48:12; 58:9-59:2.

25 Ex. 9 - Colditz Deposition at 49:15-21; 59:12-61:4.

26 Ex. 9 - Colditz Deposition at 60:4-21.

lesions in their breasts -- lesions that were unknown and undetected.[27] Those lesions (if they are hormone-dependent) can grow into cancer only through promotion of growth by hormones.[28] Absent hormones, these benign lesions would remain dormant or even regress.[29]

The scientific community now agrees that promotion is the mechanism by which E+P causes breast cancer.[30] E+P promotes the growth of preexisting abnormal cells or lesions, and tiny, occult cancers that would have remained clinically insignificant otherwise, into cancer.[31] As even Dr. James Pickar, Wyeth's executive in the science & research department assigned to the Prempro project admits, Prempro makes cancer cells grow bigger and become "worse."[32]

Ecological evidence reveals that breast cancer rates have followed in lock-step with changes in the rate of E+P use.[33] The Women's Health Initiative Study ("WHI") was a large-scale clinical trial designed to determine whether hormone therapy produced cardiac benefits. In July, 2002, the WHI study was abruptly and publicly terminated as breast cancer rates reached a level deemed unacceptable by researchers.[34] E+P use plummeted and within a year, so did the incidence of breast cancer.[35] The decline was concentrated in hormone receptor-positive tumors

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27 Ex. 11 - Wertheimer Exp. Rpt at 4.

28 Ex. 9 - Colditz Deposition at 60:11-61:4.

29 Ex. 9 - Colditz Deposition at 59:12-60:2.

30 See above Weinberg (Ex. 26 PX 1766); Austin (Ex. 31) p. 25-30; Klimberg Declaration (Ex. 32) at 2. Klimberg is a breast surgical oncologist and Professor of Surgery and Pathology and Director of the Breast Cancer Program at the University of Arkansas at Little Rock.

31 Colditz (Ex. 9) at 49:6-14; Ex. 5 at 227:19-23; 279:7-14; Ex. 41 at 937:16-25; 939:2-9; 975:12-24.

32 Pickar (Ex. 33) at p. 5-7; p. 44:7-45:3.

33 Austin (Ex. 31) at p. 47-50.

34 Ex. 34 - PX 8155.

35 Marshall (Ex. 35 - PX ML 5838) at p. 12 (Conclusions: Along with other studies showing similar conclusions, our data provide further evidence that recent declines in invasive breast cancer incidence in the US are explained predominantly by decreased HT use); Kerlikowske (Ex. 5 - PX ML 4854) at p. 5 (decline in E+P use contributed to the decline of breast cancer causing 17,500 fewer breast cancers each year); Ravdin (Ex. 36 - PX ML 4743)1670-1674; Banks (Ex. 37 - PX ML 5500); *Scroggin* (Ex. 20) at 254:5-256:10.

among postmenopausal women.[36] Even Wyeth, on its website, confirms this connection.[37] This dramatic drop in hormone-dependent cancers disproves Wyeth's claim that all women have enough of their own estrogen after menopause to develop breast cancer, thereby making E+P irrelevant.[38] Studies now show that an estimated 17,500 women a year avoided the development of cancer solely by not taking E+P.[39] These hormone deficient women did not produce enough natural hormones to feed a cancer. Further, E+P increases the breast's production of estrogen[40] and increases the amount of estrogen present in the actual breast tissue by 18 times the normal post-menopausal level and 7 times the pre-menopausal level.[41] E+P swamps the breast with the exact hormones needed to grow and develop hormone-dependent breast cancer.

Wyeth claims the WHI study found only a small incidence of breast cancer, in particular, a 1.24 relative risk. That position ignores that (a) the WHI study was terminated prematurely because of the high incidence of breast cancer after average use of only 4.4 years and (b) the WHI had a 40 percent drop-out rate.[42] Controlling for these factors, and considering prior use by study participants, WHI investigators adjusted their original estimates and found a greater than

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36 Ex. 11 Wertheimer Expert Report at 7-8.

37 Ex. 38 - PX 1055 (p. 1 –" Fewer women are using HRT, which may explain why new cases of breast cancer among postmenopausal women have declined.."; p. 4 – "As further evidence of the association between HRT and breast cancer, a 2007 New England Journal of Medicine study noted that breast cancer rates have fallen as HRT use has declined. The decline in rates occurred among women over the age of 50 and was particularly associated with cancers that were estrogen receptor-positive. This type of cancer requires estrogen for growth. Experts think that postmenopausal women's discontinuation of estrogen-containing HRT may explain the decrease in rates of new cases of estrogen receptor-positive cancer.")

38 See Wyeth's Memo. in Support of Defendant's Consolidated *Daubert* Motion at 14.

39 See above, Ex. 5 - PX ML 4854 (Kerlikowske)

40 Stute (Ex. 39 - PX ML 5060) at 1, 6.

41 Chatterton (Ex. 40 - PX ML 2488).

42 Austin (Ex. 20) at 197:11-198:25; 214:22-215:10.

tripling of the risk among those using the drugs for five years or more.[43] The Eighth Circuit cited this finding in *Scroggin*, 586 F.3d at 561.

B. Dr. Michael Wertheimer Is Qualified to Opine on Causation and the Various Evidence Supporting His Conclusions.

Dr. Michael Wertheimer is Associate Professor of Surgery at Harvard Medical School and Associate Chief of the Department of Surgery at Cambridge Hospital. After attending medical school at the University of Pennsylvania, Dr. Wertheimer received his surgical training at the Harvard training program at Beth Israel Hospital in Boston. He practiced there before joining the surgical faculty at the University of Massachusetts. He is board certified and has been recertified three times. He was director of the New Massachusetts Breast Center for 25 years. For the past four years, he has directed the Cambridge Breast Center which he founded. He remains clinically active in all aspects of breast care management.[44]

Wyeth argues that Dr. Wertheimer is not qualified to testify about anything other than how to treat breast cancer because that is his specialty.[45] Neither *Daubert* nor Rule 702 has ever been so circumscribed. As long as the physician has "specialized knowledge" that will "assist the trier of fact," his testimony is admissible. FED. R. EVID. 702. "The proffered expert need not be a specialist in a particular medical discipline to render expert testimony relating to that discipline." *Gaydar v. Sociedad Instituto Gineco-Quirurgico y Planificacion*, 345 F.3d 15, 24 (1st Cir. 2003).

In fact, courts have found a variety of medical experts qualified to testify in areas diverse from their own specializations. *Mitchell v. United States*, 141 F.3d 8, 15 (1st Cir. 1998) (finding internist with specialty in hematology and oncology qualified to opine on standard of care for

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43 Ex. 20 - Austin, Scroggin Trial Transcript at 202:11-203:9.

44 Ex. 11 - Wertheimer Expert Report at 1; Wertheimer (Ex. 42) at 26:15-27:24; 28:14-22.

45 Wyeth's Daubert Memo at 8, 17.

gastroenterologist performing a colonoscopy)); *Huss v. Gayden*, 571 F.3d 442, 455 (5th Cir. 2009), *cert. denied*, 130 S. Ct. 1892 (Mar. 22, 2010) (finding internist specializing in internal medicine qualified to testify as to cause of cardiomyopathy despite having no specialty in cardiology or toxicology [46] Such experts may not only rely upon, but may testify about, information from other disciplines they considered, especially if they routinely rely upon such materials. *See, e.g., Holbrook*, 80 F.3d at 782 (holding that physician may testify about a pathology report even though not a pathologist).

> [E]xclusion was not the proper remedy "simply because the experts did not have the degree or training which the district court apparently thought would be most appropriate.

In re Paoli R.R.Yard PCB Litig., 35 F.3d 717, 741 (3d Cir. 1994) ("*Paoli II*"), *cert. denied*, 513 U.S. 1190 (1995) (citation omitted).

"Differences in expertise bear chiefly on the weight to be assigned to the testimony by the trier of fact, not its admissibility." *Huss v. Gayden*, 571 F.3d at 452; *accord Holbrook*, 80 F.3d at 782. Dr. Wertheimer testified that he relied upon epidemiological and other data in his analysis.[47] There is no reason he should not be allowed to testify about that data.[48] As shown below, Dr. Wertheimer's practice regularly involves evaluating both the cause of breast cancer and whether E+P is responsible for individual cases.

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[46] *See also Holbrook v. Lykes Bros. S.S. Corp.,* 80 F.3d 777, 783 (3d Cir.1996) (finding physician specializing in internal and pulmonary medicine qualified to opine on radiation causing mesothelioma despite not specializing in cancer or radiation); *McCullock v. H.B. Fuller Co.*, 61 F.3d 1038, 1043 (2d Cir. 1995) (finding otolaryngologist qualified to testify that industrial fumes caused plaintiff's throat polyps despite not being certified in environmental medicine).

[47] Ex. 27 - Wertheimer Depo (7/14/10) at 22:12-23:8.

[48] In his deposition, when Dr. Wertheimer began explaining why Wyeth's lawyer's questions about epidemiology were too simplistic, the Wyeth lawyer cut him off and never returned to the subject (See Ex. 27 - Wertheimer Depo (7/14/10) at 18:10-19:5).

C. Differential Diagnosis Is a Scientifically Valid Methodology for Ascertaining Whether E+P Was the "But For" Cause of an Individual Woman's Breast Cancer.

Differential diagnosis "has widespread acceptance in the medical community, has been subject to peer review, and does not frequently lead to incorrect results." *Westbury v. Gislaved Gummi AB*, 178 F.3d 257, 262-63 (4th Cir. 1999); *see also Glaser v. Thompson Med. Co.*, 32 F.3d 969, 978 (6th Cir. 1994) (differential diagnosis is "a standard diagnostic tool used by medical professionals to diagnose the most likely cause or causes of illness, injury and disease"); *Heller v. Shaw Indus., Inc.*, 167 F.3d 146, 154-55 (3d Cir. 1999) ("differential diagnosis consists of a testable hypothesis, has been peer reviewed, contains standards for controlling its operation, is generally accepted, and is used outside of the judicial context"). "The overwhelming majority of the courts of appeals" concur. *Westbury*, 178 F.3d at 263 (multiple citations omitted).

Contrary to Wyeth's claim, the fact that the use of differential diagnosis in a particular context has not been the subject of peer-reviewed articles is not fatal to an expert's testimony.[49] The Supreme Court has expressly acknowledged that peer-review publication is not a prerequisite to admissibility. *Daubert*, 509 U.S. at 593-94. Furthermore, it is unrealistic to expect that each application of differential diagnosis will be the subject of publication given the universal support the methodology already enjoys. *In re Paoli R.R. Yard PCB Litig.*, 35 F.3d 717, 758 (3d Cir. 1994), *cert. denied*, 513 U.S. 1190 (1995).

Courts have routinely approved differential diagnosis as a means to determine a cause of cancer in individual cases. *See, e.g., Wicker v. Consolidated Rail Corp.*, 371 F. Supp. 2d 702, 728-29 (W.D. Pa. 2005) (toxic chemicals and lung cancer); *Hall v. Babcok & Wilcox Co.*, 69 F. Supp. 2d 716, 721 (W.D. Pa. 1999) (nuclear radiation and various cancers). This includes breast

[49] Wyeth's *Daubert* Memo at 9, 10.

cancer. *Beck v. Koppers, Inc.*, 2006 WL 270260, at *10-11 (N.D. Miss. Feb. 2, 2006); *see also In re Silicone Gel Breast Implants Prods. Liab.. Litig.*, 318 F. Supp. 2d 879, 917 (C.D. Cal. 2004) (expert did not rule out other causes of breast cancer but proved them less likely).

Wyeth suggests that an expert cannot merely say he has performed differential diagnosis and escape scrutiny.[50] But the cases Wyeth cites state that an expert's failure to rule out all alternative causes goes to the weight, not admissibility, of the testimony. *See, e.g., Cooper v. Smith & Nephew, Inc.*, 259 F.3d 194, 202 (4th Cir. 2001). Unless the expert refuses to consider alternative causes, the testimony should not be excluded. *Id.*

Differential diagnosis is such an accepted method for determining causation that it is taught to medical students and appears in basic textbooks. *See, e.g.,* A. MCGEHEE HARVEY, ET AL, THE PRINCIPLES AND PRACTICE OF MEDICINE 2-3 (Appleton-Century-Crofts New York 1980). Differential diagnosis is often used to assess the relationship between disease and external factors such as medicines or workplace exposures.[51]

Wyeth claims Dr. Wertheimer invented this methodology for litigation.[52] To the contrary, Dr. Wertheimer has long used differential diagnosis to ascertain the likely cause of a patient's breast cancer.[53] And he is not alone. Treating physicians of other Prempro victims (physicians who are unpaid third parties and have no dog in this hunt) have similarly determined that

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50 Wyeth's *Daubert* Memo at 18.

51 FEDERAL MANUAL ON SCIENTIFIC EVIDENCE (Ex. 22) at 443-444, 468-469.

52 Wyeth's *Daubert* Memo at 9-10.

53 Wertheimer (Ex. 42) at 75:18-23 and 34:1-23; Wertheimer (Ex. 27) at 39:2-40:18; Wyeth claims Dr. Wertheimer's failure to tell a patient that hormone therapy caused her breast cancer somehow rebuts his testimony (Wyeth's *Daubert* Memo at 9). But Dr. Wertheimer explained that surgeons do not typically tell the patient what they believed caused the cancer; they tell the patient what she must endure to overcome the cancer and identify the probable cause in the patient's history on her chart. Wertheimer (Ex. 27) at 45:16-46:14; 50:11-21.

hormone therapy caused their patients' breast cancers.[54] At the Cambridge Breast Cancer Weekly conferences where Dr. Wertheimer and his colleagues examine individual cases, on multiple occasions, the physicians have isolated E+P as the cause of a woman's breast cancer.[55] Dr. Wertheimer testified that surgeons use differential diagnosis every day to determine the likely cause of an individual's breast cancer.[56] Differential diagnosis is an appropriate and generally accepted means of determining whether E+P caused a particular patient's breast cancer.[57]

This methodology is important to determining appropriate treatment options. Dr. Naftalis, a breast surgeon, has testified that she regularly employed differential diagnosis in her private practice.[58] Dr. Naftalis testified that differential diagnosis is important to a breast cancer treating physician to determine the appropriate course of treatment and prevention.[59] Treatment will vary depending upon what the physician determines was the likely cause of breast cancer. For instance, a tumor caused by genetics might require more aggressive surgery than other tumors.[60] A tumor caused by hormone therapy would be treated by cessation of E+P and administration of an estrogen blocking drug.[61] A tumor initiated by radiation would be treated by breast conservation rather than chemotherapy or radiation.[62] Dr. Klimberg concurred in this assessment.[63]

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54 Diab (Ex. 43) at p. 11; 32:19-21; 87:11-88:22; Gilbert (Ex. 44) at 27:16-29:14.
55 Wertheimer (Ex. 27) at 49:17-50:16.
56 Wertheimer (Ex. 27) at 41:4-42:6, 250:13-251:7.
57 Wertheimer (Ex. 42) at 75:18-76:1.
58 Ex. 41 at 961:7-962:18; Naftalis (Ex. 45) at 79:3-81:8.
59 Ex. 46 at 74:16-75:23; Ex. 41 at 861:7-21, 962:12-963:14.
60 Ex. 46 at 57:18-58:16.
61 Ex. 46 at 59:8-16; Diab (Ex. 43) at p. 65-67.
62 Ex. 46 at 59:17-22; Ex.41 at 963:7-19.
63 Klimberg (Ex. 32) at 1-2.

Physicians specializing in breast cancer treatment agree that differential diagnosis is a regularly employed methodology by doctors who treat breast cancer and enjoys widespread acceptance in the medical community. In addition to the physicians cited above, such physicians include Drs. Richard Hirschman (medical oncologist trained at John Hopkins, Sloan Kettering and Columbia), Paul Goldfarb (surgical oncologist trained at Albert Einstein and former president of the California chapter of American Cancer Society), Roy MacKintosh (medical oncologist trained at MIT and Stanford and Director of Oncology at the University of Nevada Medical School), (James Waldron (pathologist trained at Vanderbilt and former professor at Yale) and Rene Rubin (oncologist / hematologist and private practice physician in Pennsylvania).[64] Even treating physicians called as fact witnesses, who have no interest in the litigation, concur.[65]

The fact that Wyeth has retained experts who disagree does not make Dr. Wertheimer's testimony inadmissible because evaluating competing expert testimony is the province of the jury. *Quiet Technology DC-8, Inc. v. Hurel-Dubois UK Ltd.*, 326 F.3d 1333, 1341 (11th Cir. 2003). Furthermore, Wyeth's experts' conduct outside the courtroom belies their litigation claims. Dr. David Ling, a retained Wyeth expert, after criticizing the plaintiff's methodology in a *Frye* hearing in Philadelphia, admitted on cross-examination that he employed differential diagnosis to determine whether a drug had caused a particular patient's seizure, and published his results, even though we do not know all the causes of seizures.[66]

Wyeth's claim that no one can isolate a potential cause of breast cancer belies reality. Within academia, the pharmaceutical industry and drug safety government agencies like the

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64 Ex. 47 to Ex. 50 - Affidavits of physicians from around the country.

65 Diab (Ex. 43) at p. 87:11-88:22; Gilbert (Ex. 44) at 27:16-29:14.

66 Ex. 51 at p. 60-80; Ling (Ex. 52); Wertheimer (Ex. 27) at 254:8-255:6.

FDA, there are established protocols for establishing causation of an adverse event such as cancer. For example, the Devita Cancer textbook sets out the factors to consider in evaluating the causes of cancer.[67] A published review of the methods to monitor adverse drug reactions (ADR) sets forth the role of causality assessment in this process.[68]

So well accepted is this methodology that the FDA has published guidelines for the drug industry to follow in making these assessments.[69] And Wyeth even has a specific published protocol for its safety physicians to use to assess the likelihood that its drug was connected to the development of breast cancer in the volunteers for Wyeth's clinical trials. [70] Following virtually identical differential diagnosis methodology as employed by Dr. Wertheimer, Wyeth's safety surveillance doctors have assessed E+P's relationship to the development of breast cancer over 50 times.[71] Wyeth has even assessed that some of those breast cancers were related to the patient's use of E+P.[72] The academic literature also reflects use of these same methods.[73] A typical causality assessment evaluates the potential causes of an injury and gives a probabilistic opinion of the role that the drug in question played. Such assessments exist for a wide variety of illnesses, including a number of illnesses for which all risks or causes are still not known, including a connection between hormones and breast cancer, specifically.[74] Wyeth employs the

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67 DeVite (Ex. 53) p. 185.

68 Palaian (Ex. 54 PX ML A6001) 119-127; *see also* Jones (Ex. 55 - PX ML 6000).

69 FDA's Guidance for Industry (Ex.56 - PX 8031).

70 Wyeth's Admin. Policy (Ex. 57 - PX 1680) at p. 8-9, 12.

71 Pickar (Ex. 33) at p. 88:1-108:11; Pickar (Ex. 58) at p. 52:13-56:4.

72 See last footnote; Ex. 59 - Graphic depiction of Wyeth's causality assessments; Ex. 60 - PX 285A at p. 4 (breast cancer assessed as possibly related to use of Prempro); Ex. 61 - PX 21004 (Patient # 30902-0022: possibly related; Patient # 30908-0023: possibly related); Ex. 62 - PX 21032A (breast cancer related to E+P); Ex. 63 - PX 21031K (breast cancer assessed by investigator as definitely related to E+P drug)

73 Narango (Ex. 64).

74 ALERT Serious Event (Ex. 65 PX 20098) (causality assessment of MPA and tremor concluding that the drug was a "possible" cause of the neurological disorder); Stein E-Mail (Ex.

very practice it criticizes here.[75] When employing this same methodology, Wyeth has actually found a causal relationship between E+P and breast cancer on many occasions.[76]

D. Dr. Wertheimer Excluded All Potential Causes of the Promotion of Plaintiff's Breast Cancer other than E+P by Determining Plaintiff Had No other Tangible Source of Hormones.

Hormone receptor-positive tumors, like the one suffered by plaintiff, require hormones to grow. Thus, an appropriate differential diagnosis isolates the source of the hormones fueling the tumor's growth. As the Eighth Circuit held:

> [P]ublished research had concluded that hormone-receptor-positive tumors need hormones to grow, that menopausal symptoms result from hormone deficiency, and that there is a link between breast cancer and hormone replacement therapy.
> * * *
> Dr. Naftalis was able to testify that Scroggin's breast cancer would not have developed without hormone replacement therapy because Scroggin's body was not producing sufficient amounts of hormones to allow hormone-receptor-positive tumors to develop. Thus, Dr. Naftalis ruled out the other possible cause of Scroggin's breast cancer, and her expert testimony was properly admitted.

Scroggin, 586 F.3d at 566, 567 (attached as Ex. 1).

1. Plaintiff's breast cancer was hormone receptor-positive.

Pathologists testing plaintiff's tumor determined that it was positive for the presence of both estrogen receptors and progesterone receptors.[77]

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66 PX 10659) (causality assessment report of norethinclrone acetate/ethinyl estradiol and breast cancer concluding that the breast cancer is a serious event and that it is considered related to the drug (nor ethindrone-ethinyl estradiol); Stein Ltr (Ex. 67) (causality assessment of norethindrone acetate/ethinyl estradiol and breast cancer concluding the event was most likely an intercurrent illness yet a contribution of the drug could not be excluded); Belmonte (Ex. 68 PX ML 6002) (causality assessment of Cabergoline and pleuropulmonary toxicity concluding that the drug exposure was "probably" related to the lung condition).

[75] Ex. 69 - Affidavit of Dr. Michael Wertheimer at 1-2.

[76] Ex. 59 - Graphic depiction of Wyeth's causality assessments.

[77] Ex. 70 - Pathology Report of Georgia Torkie-Tork.

2. Plaintiff's hormone receptor-positive tumor depended upon hormones for its growth.

In addition to Dr. Wertheimer, Wyeth as well as Drs. Colditz and Naftalis agree that an ER+/PR+ tumor is one that requires hormones to fuel its growth.[78] As Wyeth's website explains, hormone receptor positive breast cancer "requires estrogen to grow." The National Cancer Institute confirms that hormone positivity in a cancer means that the cancer must have hormones to grow:

> ***Hormone receptor test***: This test shows whether the tissue has certain hormone receptors. Tissue with these receptors needs hormones (*estrogen* or *progesterone*) to grow.[79]

On the oncology website for the Abramson Cancer Center of the University of Pennsylvania, Dr. Kevin Fox, assistant director for clinical affairs, explains that hormone receptors are proteins and "the presence of these proteins means that the cancer requires estrogen for its growth."[80] Dr. Robert Weinberg, a distinguished cancer biologist, wrote in his textbook, *The Biology of Cancer*, that estrogen is "critically important" to the development of an ER-positive tumor."[81] Dr. Klimberg testified that hormone receptor-positive tumors must have hormones to grow.[82] This is true for all hormone-dependent tumors, regardless of their origins (even if they are the product of the proverbial unknown "X" factor).[83]

Wyeth claims other growth factors can feed a tumor.[84] Initially, disagreement among experts does not warrant exclusion under *Daubert*, as shown above. Further, Wyeth fails to

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78 Wyeth's Website (Ex. 6 - PX 10555) at p. 4; Colditz (Ex. 9) at 174:11-175:4; Ex. 46 at 972:25-973:15; 1077:7-8.

79 Ex. 71 - PX 8426A - National Cancer Institute**.**

80 Ex. 72 - PX 20269 - OncoLink.

81 Ex. 73 - PX 8080 - Weinberg, *The Biology of Cancer*.

82 Klimberg (Ex. 74) at 1729:18-21 (cannot have hormone-dependent breast cancer without hormones).

83 Klimberg (Ex. 75) at 1511:15-1512:7.

84 Wyeth's *Daubert* Memo at 11-12.

distinguish between factors promoting the growth of already established cancers versus factors that cause benign lesions or occult cancer cells to develop into clinical cancer. Once a malignancy has developed, the cancer can become hormone-independent. But the cancer, if hormone receptor-positive, would not have developed in the first place without hormones because such tumors require hormones for growth from whatever abnormality existed before E+P to the clinically diagnosed cancer.[85] Moreover, alternate growth factors are actually dependent on estrogen.[86]

Wyeth claims the fact that men who acquire breast cancer generally acquire hormone receptor-positive cancer means estrogen cannot be critical to such tumors' growth.[87] But men rarely get breast cancer because they rarely possess sufficient estrogen to fuel tumor growth.[88] And the men who do develop hormone-dependent breast cancer typically have unique factors or conditions that dramatically increase their levels of hormones.[89]

Wyeth claims that plaintiff ingested E+P for only three years and insufficient evidence establishes causation for less than five years use.[90] First, Wyeth is wrong factually – plaintiff used E+P for at least five years.[91] Wyeth claims plaintiff's testimony is contradictory so the Court must rely on prescription records alone.[92] Ignoring that Wyeth offers no legal support for such an odd claim, plaintiff testified she began taking E+P in 1996 or 1997. The prescription

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85 Wertheimer (Ex. 11) at 9; Ex. 76 at 11; Naftlais (Ex. 77) at p. 111:4-13.
86 Wertheimer (Ex. 11) at 9; Dew (Ex. 78) at 152; Naftalis (Ex. 77) at 87:23-88:15.
87 Wyeth's *Daubert* Memo at 11-12.
88 Ex. 27 - Wertheimer Depo at 192:9-14.
89 Austin (Ex. 79) at 75:22-76:76:21; Naftalis (Ex. 80) at 14:4-15:5.
90 Wyeth's *Daubert* Memo at 15.
91 Ex. 81 - Plaintiff Depo at 157:12-16; 212:14-21.
92 Wyeth's *Daubert* Memo at 4-5 n. 16

records do not reflect samples plaintiff received from Dr. Joel Schulman.[93] There is no dispute that her use extended through much of 2002.[94] Taking even 1997 as a start date, Plaintiff was exposed to E+P for more than 5 years.

But even if plaintiff's use were limited to three years, substantial epidemiological evidence supports causation, establishing even a 2.0 or greater relative risk (which, again, is sufficient by itself to establish specific causation).[95] The Million Women Study ("MWS"), the largest hormone therapy study conducted to date, established a 2.0 RR for women who used E+P for 2.6 years.[96] In a re-analysis of the WHI data, Dr. Garnet Anderson reported that the relative risk reaches 2.0 at less than four years use.[97] Wyeth previously moved the MDL court to exclude expert testimony that less than five years use causes breast cancer and the court denied the motion in the case of a woman who used E+P for just over three years.[98] Further, the ecological data showing declines in breast cancer rates in just one year after E+P use plummeted following WHI establishes that causation in many women occurs within months of use rather than years.[99]

3. <u>Plaintiff was hormone-deficient and thus not producing sufficient hormones naturally to fuel the growth of her cancer.</u>

While all women experience a substantial decline in hormone production during menopause, many women continue to produce significant levels of natural hormones. These women produce enough of their own estrogen to fuel the growth of a hormone-dependent

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93 Ex. 81 - Plaintiff Depo at 151:1-19. Dr. Schulman did not deny that he may have provided these samples (Ex. 82 - Schulman Depo at 68:15-69:12).

94 Wyeth's *Daubert* Memo at 4-5.

95 Wertheimer (Ex. 11) at 5-6; Calle (Ex. 83 - PX ML 5011) p. 936 (risk from E+P increased within 2 to 3 years of use); Prentice (Ex. 84 - PX ML 5167) at p. 4, 6 (Table 4: Hazard ratios were elevated after the first 2 years of E+P use, RR for 2-5 years of use = 2.01); Colditz (Ex. 85 - PX ML 4989) (E+P causes "an increase in risk in the initial 2 to 5 years of use."); Jick (Ex. 17 - PX ML 4977) (Relative risk of 3.10 for two or more years of use).

96 Beral (Ex. 18 - PX ML 79) at 1.

97 Anderson (Ex. 86 - PX ML 3406) at 8.

98 Order (Ex. 87) at 2-3.

99 Colditz (Ex. 9) at 54:7-18; Colditz (Ex. 88) at p. 795:4-796:2.

cancer.[100] However, a minority of women suffer from significant menopausal symptoms, a clear marker that they have become estrogen deficient.[101] By Wyeth's calculations, only 17.5% of women develop such symptoms. Wyeth's hormone drug label thus confirmed that "most women have no or only mild menopausal symptoms and do not need estrogens."[102] These women no longer produce sufficient natural hormones to fuel the growth of hormone-dependent abnormal cells into cancer, as shown below.

Plaintiff was hormone deficient as she entered menopause. She suffered from vasomotor symptoms of menopause, in particular, hot flashes and night sweats "all the time," as Wyeth concedes.[103] Menopausal symptoms, such as hot flashes, are markers for hormone deficiency.[104] Wyeth's own literature confirms this. [105] E+P treats menopausal symptoms precisely because the symptoms are caused by estrogen deficiency.[106] And as for Georgia Torkie-Tork, her hot flashes were relieved by Prempro which confirms that low natural hormones were the cause of this symptom.[107]

Wyeth argues that some articles dispute the link between estrogen deficiency and hot flashes. First, a conflict among scientists does not make expert testimony inadmissible, as shown above. Second, Wyeth's own documents and experts agree that hot flashes are the product of

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100 Ex. 76 at 6-7.

101 Ex. 89 - PX 1206 – Wyeth's survey (7/22/91).

102 Ex. 90 - PX 6483A (1998 Premarin Label).

103 Wyeth's *Daubert* Memo at 3-4; Wertheimer (Ex. 11) p. 12; Plaintiff (Ex. 81) p. 144-150.

104 Ex. 27 - Wertheimer Depo. at 50:22-52:9; Ex 8 at 6-7.

105 Wyeth-Ayerst (Ex. 91 - PX 6093); McNagny (Ex. 92) (article sponsored by Wyeth); Notelovitz (Ex. 93 - PX ML 5471) at p. 6 (Estrogen deficiency has a central role in the pathogenesis of hot flashes); Yasui (Ex. 94 - PX ML 3567) at p. 2 (Low natural hormone levels in post-menopausal women were related to appearance of hot flushes).

106 Ex. 27 - Wertheimer Depo. at 53:16-22; Ex. 32 at 210:13-211:17.

107 Ex. 81 - Plaintiff Depo at p. 166-167; p. 270.

estrogen deficiency.[108] The Eighth Circuit rejected precisely Wyeth's argument here for these reasons:

> Although Wyeth presented evidence disputing this association [between menopausal symptoms and estrogen deficiency], the factual basis of an expert opinion is assessed by the jury, and the jury may have been persuaded by Wyeth's own documents, asserting a link between estrogen deficiency and uncomfortable menopausal symptoms.

Scroggin, 586 F.3d at 566 n. 12.

Third, Wyeth's argument ignores the effect of E+P on a woman's hot flashes. Dr. Wertheimer acknowledges there are other causes of hot flashes. Hot flashes suggest hormone deficiency when they are alleviated by hormone therapy. In other words, if hormone therapy makes the hot flashes go away, the flashes were caused by hormone deficiency – which is precisely what happened with Georgia Torkie-Tork.[109]

Finally, Wyeth's articles are based on circulating estrogen (i.e., serum levels of estrogen), not the estrogen affecting actual tissue.[110] A woman's production of hormones declines after menopause when the ovaries essentially shut down. Estrogen-sufficient women produce substantial hormones through other organs. This production may or may not spill over into the bloodstream, but the spillover does not indicate the level of estrogen reaching tissue. Dr. Chatterton's nipple aspirate study confirms that E+P dramatically increases the levels of hormones in the actual breast tissue (18 times the pre-menopausal levels).[111]

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[108] Ex. 95 - PX 497 at p. 2 – Wyeth marketing document (Estrogen loss can result in many different effects including menopausal symptoms, such as hot flashes and night sweats); Ex. 96 - PX 378 (Menopause and its associated estrogen loss can lead to potentially serious medical conditions including hot flashes); Langer (Ex. 97 - PX 20258C) at p. 61-64; Creasman (Ex. 98 - PX 20258A) at p. 208-209.

[109] Ex. 27 - Wertheimer Depo at 52:24-53:22; 77:4-85:1.

[110] Ex. 27 - Wertheimer Depo at 77:4-78:24.

[111] Ex. 40 - PX ML 2488 – Chatterton (see above).

Wyeth claims that Dr. Wertheimer impugned hot flashes as an indicator of hormone deficiency in his deposition.[112] Dr. Wertheimer testified only that urogenital symptoms are a stronger indicator because hot flashes are transitory; they generally occur for a brief period at the onset of menopause.[113] Thus, some studies show no relationship because estrogen deficient women in the studies ceased having hot flashes long ago. Plus, there are other causes of hot flashes. The key inquiry, Dr. Wertheimer testified, is whether E+P alleviates hot flashes. If it does, the hot flashes were the product of hormone deficiency. [114]

Real world experience confirms Dr. Wertheimer's assumptions. First, low levels of estrogen produce very low incidence of breast cancer, particularly hormone receptor-positive cancer. For example, removal of a woman's ovaries, the body's primary estrogen-manufacturers, causes "breast cancer risk to plummet."[115] Premature menopause brought on by the side-effects of chemotherapy for Hodgkin's lymphoma results in a 90 percent reduction in breast cancer risk.[116] Studies on estrogen-blocking drugs, like Tamoxifen and Raloxifene, provide compelling proof that hormone-positive tumors do not grow or survive without hormones.[117] Not only do drugs that block a woman's exposure to hormones prevent existing cancers from growing or recurring, they can prevent cancer from forming in the first place. The National Cancer Institute's Tamoxifen study showed that blocking hormones in a woman's body reduces the occurrence of estrogen receptor-positive tumors by 69 percent. Even more significantly, this estrogen-blocking drug decreases the incidence of breast cancer among women

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112 Wyeth's Daubert Memo at 12-13.
113 Ex. 27 - Wertheimer Depo at 52:24-53:10.
114 Ex. 27 - Wertheimer Depo at 53:16-22; Ex. 11 - Wertheimer Exp. Rpt at 10.
115 Ex. 73 - PX 8080 - Weinberg, *The Biology of Cancer*; Ex. 11 - Wertheimer Exp. Rpt at 5.
116 Weinberg Textbook at 440-41.
117 Fisher (Ex. 99 - PX ML 3867); Cummings (Ex. 100 - PX ML 2849).

known to have abnormal breast cells (women with a history of atypical hyperplasia) by a staggering 86 percent.[118]

The Journal of the American Medical Association reported that a study involving administration of Raloxifene, an estrogen-blocker, reduced the incidence of estrogen receptor-positive breast cancer by 81 percent in women with the highest levels of estrogen and had no discernable effect on women with undetectable estrogen levels (as these women were already at a low risk of breast cancer).[119]

Second, women suffering from vasomotor symptoms of menopause have substantially lower breast cancer incidence. Even Dr. Cummings, Wyeth's consultant, agrees with this premise.[120] The ATAC (Arimidex, Tamoxifen, Alone or in Combination) study reported that women administered anti-estrogen drugs to prevent breast cancer from returning, and who experience vasomotor symptoms as a result, had a 50 percent lower recurrence of breast cancer than women without such symptoms.[121] The WHEL (Women's Healthy Eating and Living) study focused on hot flashes and likewise found a 50 percent reduction in breast cancer risk among women administered Tamoxifen (an estrogen blocker) who reported hot flashes. [122]

These studies underestimate the lower risk of women with symptoms because the studies looked at women who already had breast cancer. As noted above, once cancer is established, it can find different pathways to growth. But in the developmental stage, a lesion that ultimately

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118 Fisher (Ex. 99 - PX M3867).

119 Ex. 100 - PX ML 2849 (Cummings). Dr. Wertheimer relied on such studies in forming his opinion (Wertheimer Depo (Ex. 27) at 44:10-21; Wertheimer Exp. Rpt (Ex. 11) at 5.

120 Ex. 101 - PX 20262 - Deposition of Dr. Cummings (6/11/10) at p. 67; 154-156.

121 Cuzick (Ex. 102 - PX ML 6000) at 1143-48 (Dec. 2008); Crandall (Ex. 103 - PX ML 532) at 1688-89.

122 Mortimer (Ex. 104) 108:421-426 at Table 2.

becomes a hormone receptor-positive tumor must have hormones to grow.[123] Thus, the rates of cancer in symptomatic women who have not yet had cancer are much lower.

Wyeth claims all this evidence is insufficient because Dr. Wertheimer admitted "it is possible" that plaintiff could have developed breast cancer without taking E+P.[124] Initially, plaintiff's burden is not to prove beyond a reasonable doubt that E+P caused her breast cancer. Her burden is proof by the preponderance of evidence. *Parham v. Albert*, 418 S.E.2d 866, 868 (Va. 1992). This means she must prove causation is more likely than not true "notwithstanding any doubts that may linger." *Lamar Co. v. Bd. of Zoning Appeals*, 620 N.E.2d 753, 756 n. 5 (Va. 2005). Dr. Wertheimer has clearly stated that E+P was the "but for" cause of plaintiff's cancer to a reasonable degree of medical certainty, which means more likely than not.[125]

Wyeth notes that blood tests showed that plaintiff was not estrogen deficient when she had a fertility examination in 1998.[126] Initially, Wyeth's evidence is a serum blood level test which is inherently unreliable, as noted above. But more significantly, the test result is not surprising since plaintiff had been on E+P for at least a year by then.

Wyeth claims that most postmenopausal women have vasomotor symptoms. Ignoring for a moment that this contradicts Wyeth's representations to the medical community,[127] the relevance is unclear. Wyeth appears to be asserting that this is inconsistent with the fact that the majority of postmenopausal women who get breast cancer do not take E+P. But less than one percent of women of menopausal age get breast cancer, and nearly a third who do acquire

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123 Naftalis (Ex. 77) at 111:4-13.

124 Wyeth's *Daubert* Memo at 16-17.

125 Wertheimer (Ex. 27) at 20:10-25; Wertheimer Exp. Rpt. (Ex. 11) at 2, 13.

126 Wyeth's *Daubert* Memo at 13-14, 21.

127 Ex. 89 - PX 1206 (see above). During his deposition, Wyeth confronted Dr. Wertheimer with evidence that estimates of hot flash incidence vary widely, from 30 to 80 percent, according to the National Institutes of Health (Ex. 27 - Wertheimer Depo. at 56:22-57:6).

hormone receptor-negative tumors. Thus, the incidence of hormone-dependent tumors among women not taking hormone therapy is limited to the purported minority of women without symptoms.

Wyeth complains that Dr. Wertheimer did not rule out risk factors for breast cancer other than sources of hormones.[128] Hormones were essential to the growth of plaintiff's particular type of breast cancer. Thus, to isolate the source of hormones fueling that growth is to isolate one "but for" cause of the tumor, even though there may be other causes. Whatever initiated the first abnormal cell is undeniably a cause, but what was essential to promote the growth of that abnormal cell into cancer is certainly a "but for" cause of the woman's cancer. The Eighth Circuit rejected precisely the argument Wyeth is making here in *Scroggin*, 586 F.3d at 566-67.

Independently, plaintiff's breast density was maintained by E+P. Absent the drug, her breasts would have naturally involuted when she entered menopause. Instead, they remained dense, providing additional evidence of causation.[129] And Clomid, a fertility drug, was not a risk factor for this plaintiff. Because she had never had a child, plaintiff briefly visited a fertility doctor but quickly realized she was too old to have a child. She was prescribed one month of Clomid, which she does not recall even taking.[130] There is no evidence of any refills of the prescription.

E. Prior Court Decisions Overwhelmingly Support the Admission of Dr. Wertheimer's Testimony.

As noted in the introduction, courts in 16 cases have denied the instant motion. One of the federal court rulings was appealed. In *Scroggin*, the Eighth Circuit affirmed judgment in

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128 Wyeth's *Daubert* Memo at 15-16, 21-22.

129 Ex. 27 - Wertheimer Depo. at 162:3-23; Ex. 11 - Wertheimer Exp Rpt at 10-12.

130 Plaintiff (Ex. 81) at p. 203:7-8. Even if Wyeth were to convince the jury that plaintiff ingested a single Clomid prescription, such use hardly compares to five years of E+P ingestion.

favor of the plaintiff, rejecting Wyeth's *Daubert* challenge. The Eighth Circuit approved differential diagnosis and each of the assumptions upon which it was based.

> [P]ublished research had concluded that hormone-receptor-positive tumors need hormones to grow, that menopausal symptoms result from hormone deficiency, and that there is a link between breast cancer and hormone replacement therapy.
> * * *
> Dr. Naftalis was able to testify that Scroggin's breast cancer would not have developed without hormone replacement therapy because Scroggin's body was not producing sufficient amounts of hormones to allow hormone-receptor-positive tumors to develop. Thus, Dr. Naftalis ruled out the other possible cause of Scroggin's breast cancer, and her expert testimony was properly admitted.

Scroggin, 586 F.3d at 566, 567 (attached as Ex. 1). The Supreme Court denied Wyeth's petition for writ of certiorari.

Wyeth notes that a Minnesota intermediate court in *Zandi v. Wyeth*, No. A08-1455, 2009 WL 2151141, at *12-13 (Minn. App. July 21, 2009) (unpublished), found another hormone therapy plaintiff's expert testimony inadmissible under the unique *Frye-Mack* standards in Minnesota.[131] *Zandi* is an unpublished decision and therefore has no precedential effect. *See* MINN. STAT. § 480A.08. The Minnesota Supreme Court has eschewed reliance on unpublished opinions. *Vlahos v. R&I Const.*, 676 N.W.2d 672, 676 n. 3 (Minn. 2004). Further, the *Zandi* court repeatedly emphasized that its holding was limited to the particular record before the court (which involved almost none of the evidence cited above). *Zandi*, 2009 WL 2151141 at *5, 9. Finally, the Eighth Circuit distinguished *Zandi*:

> Although *Zandi* involves similar facts, Minnesota law requires a more conservative review of expert testimony than the liberal thrust of the Federal Rules of Evidence and relies on a variant of the standard abandoned in *Daubert.* To the extent that *Zandi* excludes an expert opinion that relies on differential diagnosis to determine the cause of hormone receptor-positive breast cancer in an individual with hormone-dependent breast cancer, we respectfully disagree.

Scroggin, 586 F.3d at 567 n. 13.

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131 Wyeth's *Daubert* Memo at 19.

II. PLAINTIFF'S LIABILITY EXPERTS: DRS. CHERYL BLUME, SUZANNE PARISIAN AND DON AUSTIN

Drs. Blume and Parisian will testify on a broad range of liability issues, including the inadequacy of Wyeth's label based on the science of the time. Wyeth erroneously claims that plaintiff's "theory" is not that Wyeth's label was inadequate based on what was known earlier but only that Wyeth should have known more by studying E+P.[132] Once again, Wyeth acts as though plaintiff here is constrained by what has transpired in some prior cases (though not all). But at least on this issue, Wyeth knows better. In her interrogatory answers and summary judgment response, plaintiff has indicated clearly that she is not only arguing that Wyeth should have known more through testing, but that Wyeth's label was inadequate based on the information available at the time. Wyeth makes no argument as to why plaintiff's experts should not be allowed to testify about the inadequacy of the label based on what Wyeth already knew.

None of Wyeth's arguments apply to Dr. Austin's testimony. As the plaintiff in *LaFerrara* stipulated, Dr. Austin will not testify regarding the standard of care. Wyeth has indicated that if plaintiff will so stipulate here, this motion will not apply to Dr. Austin.[133] Plaintiff so stipulates. Dr. Austin's liability testimony will be limited to the types of studies available and their feasibility. He will not testify as to the standard of care in the industry or whether Wyeth breached that standard. The fact that Wyeth has agreed to this stipulation confirms that the prior orders Wyeth cites only prohibited discussion of the standard of care. They did not prohibit any expert from discussing the types of studies available and whether the defendant engaged in them.

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132 Memo at 24.

133 Memo at 25 n. 90.

A. Brief History of Relevant Facts

1. The lack of study on E+P.

Wyeth argues the FDA would not have approved Prempro unless it had concluded that all necessary studies had been performed. Thus, the liability experts should not be allowed to testify that Wyeth's failure to study was negligent without citing objective criteria challenging the FDA determination. [134] This position belies the nature of the FDA's approval. Wyeth never studied the breast cancer risk of E+P.[135] And Wyeth went to extraordinary lengths to suppress and counteract any adverse breast cancer data that emerged.[136] In 1990, the FDA's advisory committee on hormone therapy concluded unanimously there was a dearth of studies on E+P and breast cancer.[137] Wyeth was forced to admit, both in 1990 and 1993 (just one year before Prempro's approval), that insufficient information about E+P's breast cancer risk was known.[138]

For over a decade preceding approval, the FDA rejected multiple Wyeth applications for a combination product on the ground there had been insufficient study on the combination. [139] In 1993, the FDA reiterated that there was insufficient study.[140] But the FDA was ultimately left with a Hobson's choice: (a) continue to deny the applications, with Wyeth declining to perform the needed studies, while doctors prescribed the combination rampantly, off-label, or (b) conditionally approve the combination, thereby giving the FDA authority to order Wyeth to study the breast cancer risk. The FDA chose the latter and, the next year, approved Prempro on

134 Memo at 27.
135 Rowatt (Ex. 105) at 1865:5-1869:21.
136 *See* Plaintiff's Opp. to Defendant's Omnibus Motion for Summary Judgment at 3-11.
137 Austin (Ex. 106) at 1292:23-1293:4; 1304:4-10; 1375:2-5; Ex. 134 PX134A at 3.
138 Ex. 106 at 450:13-19; 451:22-452:8; 459:701.
139 Ex. 107 - PX231 at 2.
140 Ex. 108 - PX239 at 1.

the express condition that Wyeth conduct a post-marketing "comprehensive investigation of the breast cancer risk."[141]

2. The MDL court orders in *Scroggin*

Wyeth notes the MDL court struck Dr. Parisian's testimony in the punitive damages phase.[142] What Wyeth fails to note is that the court repeatedly approved Dr. Parisian's testimony in the liability phase when Dr. Parisian testified that Wyeth's conduct violated FDA regulations. The court denied four Wyeth motions to strike the testimony -- motions filed before, during and after trial.[143] In the punitive phase, plaintiff's counsel sought to introduce documents highlighting the malicious nature of the conduct the jury found in the first phase. The court found that plaintiff's counsel then used Dr. Parisian solely to get those documents before the jury, without having her educate the jury on the circumstances or ambiguous contents within the documents. This is a far cry from the approach other attorneys have taken (and Scroggin's counsel used in the first phase) in which the liability experts educate the jury regarding the FDA regulatory process, define regulatory terms and explain ambiguous contents of the documents, rather than merely read excerpts from the documents.[144] In affirming judgment for the plaintiff in *Scroggin*, the Eighth Circuit repeatedly cited Dr. Parisian's liability testimony on such matters as the company's failure to heed the FDA advisory committee findings,[145] the FDA's legal

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141 Ex. 109 - PX290 at 2; Ex. 106 at 558:5-17; Ex. 105 at 1807:15-1810:13; Ex. 110 - PX287. The Eighth Circuit specifically referenced Dr. Parisian's testimony in this regard in *Scroggin*, 547 F.3d at 558.

142 Memo at 30-31.

143 *Scroggin* (Ex. 111-112) at 591:7-11; 2482:2-2483; Ex. 113.

144 See testimony excerpts attached as Exs. 114-115.

145 *Scroggin*, 586 F.3d at 558.

inability to order Wyeth to study the combination before it was approved[146] and the inadequacy of Wyeth's product labels and warnings.[147]

3. The MDL magistrate judge's recent holding

Wyeth's filings imply (if not outright misstate) that the magistrate judge excluded these experts' testimony in their entirety.[148] To the contrary, the issue before the court was a notably limited one – whether the experts could give ultimate opinions on Wyeth's breach of the standard of care.

> At the outset, the Court recognizes that this motion sets forth a very narrow issue: whether Drs. Parisian, Blume, and Austin can be designated as experts to testify about the reasonable standard of care that Defendants should have followed in the continued testing of HRT after it was placed on the market.[149]

The court then ruled that the witnesses would not be allowed to give ultimate opinions, namely that Wyeth's failure to test breached any standard of care. The court expressly declined to exclude any other testimony.[150]

4. Other court orders

Wyeth's motion has been denied in 11 separate hormone therapy trial-set cases nationwide.[151] And contrary to Wyeth's claim otherwise, the motion was not granted in *Esposito*, a Florida case. The court there expressly ordered that the experts would be allowed to testify regarding defendants' failure to test. It held only that they wouldn't be allowed to state the ultimate opinion that Wyeth's failure to test constituted negligence.[152]

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146 *Id.*

147 *Id.* at 561, 562.

148 Memo at 24-25.

149 Order (Ex. 116) at 4 (emphasis added).

150 *Id.* at 6-7 ("At present time, the Court is unwilling to preclude all testimony from these witnesses as Defendants request.").

151 Ex. 117.

152 *Esposito* Order (Memo at Ex. 49) at 3-4.

Wyeth notes that another MDL court presiding over the Trasylol litigation struck Dr. Parisian's testimony.[153] Ignoring for a moment that the record there was different, that court relied partially on the decision in *Scroggin* and clearly had not been told (as Wyeth fails to tell this Court) that the *Scroggin* court had approved Dr. Parisian's liability phase testimony.[154] Wyeth claims the Foxamax MDL court precluded Dr. Parisian's testimony,[155] but that is false. That court expressly approved precisely the kind of testimony at issue.

> The Court further finds that Dr. Parisian has followed an appropriate methodology. An expert is permitted to draw a conclusion based on extensive and specialized experience. Here, Dr. Parisian has drawn conclusions about Merck's conduct based on her review of pertinent portions of the regulatory filings for Fosamax and Merck's internal company documents. This is the methodology she applied as a Medical Officer, and Mercks's regulatory experts have followed the same methodology to prepare their reports.

In re Fosamax Prods. Liab. Litig., 645 F. Supp. 2d 164, 190-91 (S.D.N.Y. 2009) (citations omitted).[156] Just a few months ago (long after the decision Wyeth cites), the same court found Dr. Parisian's testimony probative in affirming a jury verdict for a plaintiff. The court found her testimony that Merck's failure to follow up on safety signals (precisely the testimony she will offer here about Wyeth) was probative. *In re Fosamax Prods. Liab. Litig.*, No. 1:06-MD-1789-JFK, 2010 WL 1257299, at *7 (S.D.N.Y. Mar. 26, 2010).

Other courts have followed suit. *See, e.g., In re Guidant Corp. Implantable Defibrillators Prods. Liab. Litig.*, Civil nos. 06-25, 05-2596, 2007 WL 1964337, at *8 (D. Minn. June 29, 2007) ("Dr. Parisian is allowed to testify as to...whether Guidant's actions were

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153 Memo at 31-33.

154 *In re Trasylol Prods. Liab. Litig.*, Case No. 08-MD-01928, 2010 WL 1737107, at *10 (Apr. 27, 2010).

155 Memo at 31 n. 103.

156 The court did hold that Dr. Parisian could not merely read from documents but must explain ambiguous concepts to a lay jury – a restriction with which plaintiff here has no objection.

reasonable and appropriate. Such testimony meets the requisites of Rule 702 and the evidentiary threshold required by *Daubert"*); *Lillebo v. Zimmer, Inc.*, No. 03-2919, 2005 WL 388598, at *5-6 (D. Minn. Feb. 16, 2005) ("Parisian will be permitted to testify to…[her] opinion as to whether these actions were reasonable and appropriate….Parisian offers the opinion that Zimmer could have and should have tested…prior to marketing….These opinions are clearly relevant to plaintiff's claims."); *accord Paugh v. I-Flow Corp.*, Cause No. 32D020-0802-CT9 (Henricks County, Ind.) (Apr. 19, 2010);[157] *In re: St. Jude Med., Inc. Silicone Heart Valves Prods. Liab. Litig.*, MDL No. 01-1396 (D. Minn. Jan. 5, 2004) at 35-36.[158]

Wyeth cynically suggests that Drs Parisian and Blume are interchangeable,[159] offering no citation in support of that self-serving claim. Wyeth further claims the Viagra MDL court limited Dr. Blume's testimony.[160] This is deceptive, to say the least, since that court approved precisely the type of testimony Dr. Blume will offer in this case. *See In re Viagra Prods. Liab. Litig.*, 658 F. Supp. 2d 950, 961-62 (D. Minn. 2009) ("Dr. Blume opined that there was a safety signal in 2000 that should have caused Pfizer to change its label….Pfizer's challenge to Dr. Blume's definition of a safety signal is most appropriately dealt with in cross-examination").

B. The Experts Reasonably Rely upon Their Own Experience, FDA Guidances and the Pharmaceutical Industry Code.

1. <u>The experts' testimony is admissible because it is based on their own experience.</u>

Wyeth acknowledges that Rule 702 expressly acknowledges that many experts' opinions will be based on "experience alone—or experience in conjunction with other knowledge, skill, training or education" rather than objective standards, as the MDL magistrate judge erroneously

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157 Ex. 118 - *Paugh*, slip op. at

158 Ex. 119 - *St. Jude* slip op. at 35-36.

159 Memo at 33.

160 Memo at 33.

found.[161] Wyeth claims only that such testimony must identify the experiences and how they shaped the expert's opinions.[162] Plaintiff's experts have identified precisely such experiences. The experts assert that Wyeth should have performed breast cancer studies much earlier, and they educate the jury about the various types of studies available and feasible to evaluate and quantify the breast cancer risk. For example, the experts opine that Wyeth could have done a WHI-like clinical trial much earlier. The WHI study was designed to ascertain whether hormone therapy had the cardiac benefits Wyeth had long touted.

Dr. Blume testified, for instance, that Wyeth's obligation to conduct such a study earlier was essentially the same as (a) the aspirin manufacturers' obligation to conduct a clinical trial on whether aspirin produced cardiac benefits that extended beyond their approved indications, as well as (b) the statin manufacturers' obligation to ascertain whether their products likewise had a heart benefit beyond what was approved. These manufacturers engaged in large-scale, clinical trials that mirror what Wyeth should have undertaken.[163] Dr. Parisian testified as to how the statin large-scale clinical trial suggested a duty on the part of Wyeth (and all companies in the pharmaceutical industry) to engage in a similar endeavor.[164] Plaintiff's experts do precisely what Rule 702 requires.

2. <u>The experts' testimony is admissible because it is based on FDA guidances.</u>

As Wyeth notes, the plaintiff in *LaFerrara* conceded that FDA regulations are so general that they do not contain an explicit mandate for study.[165] However, plaintiff has discovered,

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161 FED. R. EVID. 702 & adv. com. cmt.

162 Memo at 28-29.

163 Blume (Ex. 120) at 37:5-38:23; Blume (Ex. 121) at 1832:13-1834:5; Blume (Ex. 122) at 256:4-263:18.

164 Parisian (Ex. 123) at 88:3-90:13.

165 Memo at 29.

since the last *Daubert* hearing in the MDL, that the FDA has "guidances" that outline what drug manufacturers should do to satisfy FDA regulations. The MDL court has never been privy to any of the references cited in this section. An FDA "guidance" in 1995 – right after Prempro's approval -- specifically advised manufacturers that more study was needed on E+P and breast cancer. The FDA expressly asserted that observational studies that were larger than those of the past were required.[166] Dr. Parisian relied on this guidance.[167] A 2001 FDA guidance states that when a drug company submits adverse events reports, it must indicate what actions have been taken in response, including "a list of studies initiated."[168] A subsequent guidance specifically advises manufacturers that they must follow up on certain safety signals by performing observational studies.[169] These FDA guidances have not been introduced in any hormone therapy suit until now. And they clearly establish that the FDA expects manufacturers to react to safety signals with adequate studies so that the drug company can provide appropriate warnings to doctors and patients. Granted, the FDA regulations are general in nature because no one can anticipate all the specifics involved in a new drug product's introduction. But, at a minimum, they recognize the need for study, which is what plaintiff claims should have occurred.

3. The experts' testimony is admissible because it is based on industry standards.

Wyeth notes that the MDL magistrate judge excluded evidence regarding the PhrMa Code, an industry standard adopted by Wyeth.[170] But that is because Wyeth argued that

166 Ex. 124 - 1995 FDA Guidance at 1.
167 Parisian (Ex. 125) at Exhibit 17.
168 Ex. 126 - 2001 FDA Guidance at 18.
169 Ex. 127 - 2005 FDA Guidance.
170 Memo at 28; Essner (Ex. 140) (Wyeth's chief executive accepts the PhrMa Code as "the industry standard" and the standard to which Wyeth holds itself).

Arkansas law does not permit evidence of breach of industry standards to prove negligence.[171] Wyeth does not claim that Virginia law shares such an unusual tenet. Wyeth further argues that the PhrMa Code does not require study of new drug combinations.[172] By its express terms, the code states that post-marketing and surveillance studies should be scientifically based.[173] This presupposes that post-approval study is warranted. The code requires that drug company representations be based on valid scientific evidence, which necessarily includes study where existing data is inadequate.[174] Failure to ensure adequate science behind a drug violates the PhrMa Code.[175] Drug companies must continually update their knowledge, going beyond FDA regulations to ensure their products are safe.[176] And the code prohibits the off-label promotion in which Wyeth has engaged.[177] Wyeth's former CEO acknowledged these duties under the code.[178]

4. The experts' testimony involves appropriate discussion of Wyeth's documents.

Obviously, plaintiff's counsel does not intend merely to have experts read from documents (regardless of what another attorney may have done). Most juries would severely punish a party for such. Rather, plaintiff intends to have the experts discuss the label's inadequacy and explain the regulatory history of hormone therapy and terms of art or complicated concepts in documents. In contrast to drugs like Rezulin and Fen-Phen, drugs that were on the market for just a few years, hormone therapy has been marketed for 68 years. The

171 Order (Ex. 116) at 5.
172 Memo at 28.
173 Ex. 128 at 4.
174 Ex. 129 at 45:9-46:1.
175 Ex. 129 at 48:10-13.
176 *Id.* at 46:14-47:11.
177 Ex. 129 at 47:12-48:9.
178 Essner (Ex. 130) at 548-49.

drug's history and the complexity of issues surrounding it are not such that a jury can be expected to decipher thousands of pages of material, as Wyeth contends. That is why lead trial counsel in this case consistently has these experts explain the unique circumstances of FDA regulation and terms of art in pharmaceutical documents.[179]

In the welding rods MDL litigation, the defendants claimed that expert testimony the plaintiff had designated "merely offers a narrative of the case which a juror is equally capable of constructing."[180] In rejecting this claim, the court wrote:

> In this case, the great majority of the documents and articles that De. Levy is reviewing and comparing are complicated, and the inferences those documents may or may not support are not at all simple. It is through the application of his expertise that Dr. Levy may allow the trier of facts to better understand what the documents do (and don't) mean, and thus, what the defendants did (or didn't) know.[181]

Particularly relevant here, the welding rods court noted that allowing a liability expert to offer a narrative of events is particularly appropriate when there will be no "percipient" witness to explain product history or the context of the documents.[182] Wyeth will bring no witness to trial during plaintiff's case-in-chief. Thus, absent these experts' testimony, plaintiff's only option will be to introduce numerous liability documents *en masse* and discuss them for the first time in closing argument.

III. PLAINTIFF'S MARKETING EXPERT: DR. MATTHEW HOLLON

Dr. Hollon is a board certified physician specializing in internal medicine at the University of Washington in Seattle, where he is Director of Evidence-Based Medicine for the Internal Medicine Residency Program. He holds a Masters of Public Health and received a

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179 Exs. 114, 115.

180 *In re Welding Fume Products Litigation*, 2005 WL 1868046, at *17 (N.D. Ohio Aug. 8, 2005); *accord Flanagan v. Altria Group, Inc.*, 423 F. Supp. 2d 697 (E.D. Mich. 2005).

181 *Id.*

182 *Id.* at 18 n. 31.

National Research Service Award from the National Institutes of Health. Dr. Hollon will testify about Wyeth's marketing scheme and the deceptive nature of its advertising. Dr. Hollon's testimony has been found admissible in the vast majority of cases set for trial.[183]

Wyeth makes three challenges to the testimony. First, Wyeth claims the testimony will be irrelevant because none of the prescribing physicians relied on advertising.[184] To the contrary, Dr. Richard Hurwitz, plaintiff's principal prescribing physician, testified that marketing influenced not only his thinking but his decisions to prescribe. For instance, he testified that visits with company sales representatives influenced his evaluation of drugs and whether to prescribe them.[185] "Dear Doctor" letters from drug companies also influenced his decisions.[186] Even materials in the popular press and on the internet affected his thought process.[187] Dr. Hollon will testify that Wyeth's promotion of E+P exceeded acceptable standards of marketing for drug companies, thereby establishing the company's negligence.

Wyeth further complains that Dr. Hollon has testified that the similarities between two sets of advertisements are discernible to the lay person, thus Dr. Hollon's testimony is not important to the jury.[188] Wyeth's argument is misleading at best, deceptive at worse. The fact that the similarities were obvious is precisely the point. As Dr. Hollon explained, these are examples of branded and unbranded ads.[189] Branded ads are regulated; unbranded ads are not. Branded ads promote the benefits of E+P. Unbranded ads purport to discuss menopause in the abstract. It was illegal for Wyeth to promote cardiac and cognitive benefits of E+P because such

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183 *See*, *e.g.*, Orders attached as Ex. 131.
184 Memo at 35.
185 Hurwitz (Ex. 132) at 15:15-25.
186 *Id.* at 14:3-11.
187 *Id.* at 17:4-11.
188 Memo at 35-36.
189 Memo at Ex. 57, pages 30-31.

indications were not approved by the FDA and were thus off-label. So Wyeth published unbranded ads that described adverse heart and brain symptoms of menopause (ads that were unregulated). And, in the same journals, Wyeth published branded ads promoting Prempro. Both sets of ads had the same layout, the same color scheme, the same font – even the same clothes on the women depicted. In other words, it was obvious they were related. Readers would thus associate Prempro with the cardiac and cognitive symptoms of menopause – precisely what FDA regulations were designed to prevent.[190] The fact that lay people could see the similarities of the ads was part of Wyeth's scheme to circumvent restrictions on off-label promotion. But without Dr. Hollon's testimony, the jury will never know the significance of the fact that the ads were similar.

Finally, Wyeth argues that Dr. Hollon impermissibly discusses Wyeth's intent.[191] But in the very excerpts Wyeth cites, Dr. Hollon simply states that Wyeth's advertising was at odds with Wyeth's own policy and sound principles of marketing. It is up the jury to infer Wyeth's intent from this testimony. In any event, the Court can prohibit Dr. Hollon from testifying about Wyeth's intent without excluding his testimony altogether.

IV. PLAINTIFF'S RADIOLOGY EXPERT: DR. RANDALL PATTEN

Wyeth seeks two limitations on Dr. Patten's testimony, neither of which has merit. First, Wyeth claims Dr. Patten should not be allowed to testify that E+P maintained plaintiff's breast density because the decline in density was not realized until five years after she ceased taking the drug.[192] Wyeth has again overstated the evidence. Dr. Patten did not observe a decline until the

190 Ex. 133.
191 Memo at 37.
192 Memo at 39.

fifth year because mammograms for intervening years were missing.[193] Furthermore, some women do not experience a decline in the density caused by E+P for several years. Dr. Patten testified that the WHI study found lingering effects of E+P on the breast after four years cessation.[194] Wyeth relies solely on an article by Buist.[195] But that article states only that one study found that women who ceased taking hormone therapy – overall – had a tiny decrease in breast density.[196] The study did not indicate that all women experienced this decline, much less that large declines do not occur after several years. Dr. Wertheimer testified that the declines shown by the study reflected negligible decreases in breast density.[197] There is no evidence to rebut Dr. Patten's claim that cessation of E+P resulted in a decrease in plaintiff's breast density.

Wyeth further argues that Dr. Patten should not be allowed to give causation opinions because he admitted that other experts are more qualified to do so.[198] But as the case law above indicates, experts in myriad disciplines are qualified to testify regarding the cause of injury in many other fields. And the fact that an expert is not the most qualified to speak does not render his testimony inadmissible.

CONCLUSION

For the foregoing reasons, plaintiff respectfully requests that Defendant's Consolidated *Daubert* Motion be denied in its entirety. Plaintiff requests all other relief to which she is entitled.

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193 Patten (Ex. 135) at 66:11-16.

194 *Id.* at 66:17-25.

195 Memo at Ex. 60.

196 Memo at Ex. 60 at 760. Not surprisingly, the women who ceased ingesting hormone therapy experienced a return of menopausal symptoms. *Id.*

197 Wertheimer (Ex. 27) at 175:22-176:21.

198 Memo at 40.

DATED this 10th day of September, 2010.

Respectfully submitted,

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CERTIFICATE OF SERVICE

I hereby certify that on the 10th day of September, a copy of the above and foregoing was forwarded via electronic service through the ECF filing system to:

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